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Citation for published version:

MacPherson, SE, Parra, MA, Moreno, S, Lopera, F & Della Sala, S 2015, 'Dual Memory Task Impairment in E280A Presenilin-1 Mutation Carriers', *Journal of Alzheimer's Disease*, vol. 44, no. 2, pp. 481-492.
<https://doi.org/10.3233/JAD-140990>

Digital Object Identifier (DOI):

[10.3233/JAD-140990](https://doi.org/10.3233/JAD-140990)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Journal of Alzheimer's Disease

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Dual memory task impairment in E280A presenilin-1 mutation carriers

Sarah E. MacPherson^{1,2}, Mario A. Parra^{1,2,3,4,5,6}, Sonia Moreno³, Francisco Lopera³,
and Sergio Della Sala^{1,2}

¹Human Cognitive Neuroscience, Department of Psychology, University of Edinburgh,
UK

²Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, UK

³Neuroscience Group, University of Antioquia, SIU (Sede de Investigaciones
Universitaria), 62 # 52-59, Antioquia, Medellin, Colombia

⁴Scottish Dementia Clinical Research Network, NHS Scotland, UK

⁵Alzheimer Scotland Dementia Research Centre, University of Edinburgh, UK

⁶UDP-INECO Foundation Core on Neuroscience (UIFCoN), Diego Portales University,
Santiago, Chile

Word count: 4,965

Correspondence to:

Sarah E. MacPherson
Human Cognitive Neuroscience
Department of Psychology, PPLS
University of Edinburgh
7 George Square
Edinburgh, UK
EH8 9JZ
Tel: ++44 (0)131 650 9862
Fax: ++44 (0)131 651 3230
E-mail: sarah.macpherson@ed.ac.uk

Abstract

Patients with sporadic Alzheimer's disease (AD) are impaired in their ability to perform two tasks concurrently compared to healthy younger and older adults, despite being able to successfully perform the tasks on their own reasonably well. Dual task impairments have been found also in those individuals with an E280A presenilin-1 genetic mutation but who do not yet meet the criteria for AD. The aim of the current study is to determine whether this dual task deficit is specific to the given combination of tasks performed simultaneously or whether it reflects a general deficit in the ability to coordinate two tasks. Thirty-one carriers of the gene mutation who did not meet the criteria for AD and 38 non-carriers were asked to perform two memory tasks simultaneously. The familial AD carriers showed significant dual task decrements compared to those family members without the gene mutation. The findings support the notion that a deficit in the mechanism responsible for coordinating the performance of two tasks may be a clinical marker for the early detection of AD due to the E280A presenilin-1 gene mutation.

Abstract word count: 180

Keywords: dual task; working memory; familial Alzheimer disease; presenilin 1 (Alzheimer disease 3), human

Dual memory task impairment in E280A presenilin-1 mutation carriers

The ability to perform two tasks at the same time is commonly impaired in individuals in the early stages of Alzheimer's disease (AD), even though they can typically perform the two tasks on their own relatively well [1-7]. This dual task impairment is not, however, evident in healthy older adults, who are able to perform the same tasks simultaneously with very little decrement in performance on either task [1,2,4-6]. This suggests that dual task impairment is a feature of AD but not healthy adult ageing (for a discussion see [8] and [9]).

In this dual task paradigm, typically each participant performs the tasks at their own individual ability levels to ensure that the AD patients and healthy younger and older adults are matched in terms of single task performance. This ensures that any dual task impairments found in AD patients are distinct from single task differences between the patients and healthy control groups. Our previous work has also shown that the AD-related dual task decrements are not associated with the overall cognitive demands of the tasks as the dual task effect remains even when the demands of the two single tasks are reduced. In contrast, increasing the single task demands of the tasks has analogous effects on AD patients and healthy adults [4]. Moreover, as the disease progresses, the dual task impairment found in AD patients increases [1].

More recently, our work has also shown that the dual task impairment reported in sporadic AD is also evident in individuals with familial AD (FAD) due to a genetic E280A mutation in the presenilin-1 gene [10]. All carriers of this genetic mutation will develop an autosomic dominant familial AD which manifests itself clinically around 48 years of age and is similar to sporadic AD in terms of its clinical characteristics (see [11])

for a clinical description of the disease). MacPherson et al. [10] demonstrated that individuals in this large extended family who were clinically diagnosed with FAD showed dual task decrements compared to non-carriers when asked to perform a digit recall task together with a paper and pencil tracking task. Importantly, those individuals who tested positive for the genetic mutation but who did not yet meet the criteria for AD or subjectively report memory difficulties also showed significant dual task decrements compared to non-carriers. These findings suggest that the clinical manifestation of FAD may begin well before it meets the standard criteria for the diagnosis of AD and dual task decrements may be an important clinical marker of early AD.

Yet, it remains unclear whether this dual-task impairment in FAD is specific to the combination of tasks the carriers of the genetic mutation were asked to perform rather than a general impairment in a coordination mechanism responsible for performing two tasks simultaneously. To investigate this AD-specific dual-task impairment further, the current study has adopted a dual task paradigm where individuals were asked to perform two *memory* tasks simultaneously (i.e., digit recall and visual pattern recall). In this paradigm, a preload procedure is adopted to prevent any general interference from competition from sensory input or response output channels. Participants are asked to hold in memory the stimuli for one memory task (preload task) while performing the immediate recall of the other memory task (interpolated task). We have shown that sporadic AD patients also show a dual task decrement when performing two demanding memory tasks simultaneously which are adjusted for individual ability levels, and yet healthy younger and older individuals show only a small impact on the performance of each task [6,12]. In the current study, our memory plus memory dual task paradigm was

administered to those individuals who test positive and those who test negative for the genetic mutation to examine whether the carriers' dual task impairment also generalizes to the performance of two concurrent memory tasks and is due to an impairment in a coordination mechanism.

MATERIALS AND METHODS

Participants

Participants were members of a large extended family from the province of Antioquia in Colombia, South America who were enrolled in the FAD Research Program directed by the Neuroscience Group at the University of Antioquia, Colombia. Participants were genetically screened for the single mutation E280A in the preseniline-1 gene according to the Alzheimer's Disease Collaborative Group [13] methodology (see also [14,15]) and categorized as carriers or non-carriers. One hundred percent of those individuals categorized as carriers of the genetic mutation will develop early-onset familial Alzheimer's disease [11]. Three pre-dementia stages of the disease have been identified in carriers of this mutation at 35, 38 and 44 years of age [16]. Thirty-one participants tested positive for the E280A mutation (carriers) and 38 participants tested negative for the E280A mutation (non-carrier group). The carriers did not report any subjective complaints of memory difficulties and neither the carriers nor the non-carriers had any history of neurological or psychiatric disorders. All participants scored ≥ 26 on Mini-Mental State Examination (MMSE; [17]). Their genetic status was not made clear to the neuropsychologist carrying out the assessment protocol until after completion.

Table 1 demonstrates the demographic characteristics of the carriers and non-carriers. The carrier and non-carrier groups did not significantly differ in terms of their age or years of full-time education. The two groups were also matched in terms of their MMSE scores and their scores on the short form of the Yesavage Geriatric Depression Scale [18]. The research was completed in accordance with the Declaration of Helsinki.

- Insert Table 1 around here -

Background neuropsychological measures

Spanish-language versions of the background neuropsychological measures were administered to the carrier and non-carrier groups (see [19]). The following neuropsychological tests from the Consortium to Establish a Registry for Alzheimer's disease (CERAD; [20]) were administered: Mini-Mental State Examination (MMSE; [17]) to assess overall cognitive abilities, the Boston Naming Test [21] to assess naming abilities, and Memory for Words to assess episodic memory. Additional neuropsychological tests included: the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; [22]) to assess IQ and the Raven's Advanced Progressive Matrices to assess nonverbal abstract reasoning [23]. Arithmetical abilities were assessed using the Arithmetic subtest from the WAIS [24] and speed of processing was assessed using Part A of the Trail Making Test [25] and the Cancellation As Test [26]. FAS Verbal Fluency Test (adapted from [27]) and the Modified Wisconsin Card Sorting Test [28] were administered to assess executive abilities. Further episodic memory measures included

serial verbal learning [26], Paired Associates Learning Test from the Wechsler Memory Scale [29] and the Rey–Osterrieth Complex Figure Test [30,31].

- Insert Table 2 around here -

Dual task paradigm

Evaluation of Individual Ability.

Individual immediate and delayed digit and visual pattern spans were assessed for each participant as described below:

Immediate digit span. Participants were presented with sequences of digits spoken by a native Spanish speaker, at a rate of 2 digits per second. At the end of each list, participants were required to immediately recall out loud the sequences in the same order as they had previously heard them. First of all, participants were presented with three sequences of two digits and if two out of three sequences were correctly recalled, the sequence length was increased by one digit. Once individuals were no longer able to correctly remember two out of three sequences at a particular length, digit span was taken as the preceding sequence length (i.e., the maximum sequence length at which participants could correctly remember at least two out of the three sequences). There were no time limits to respond.

Delayed digit span. The same procedure to assess immediate digit span was used except there was a delay of 15 seconds between presentation of the digit sequence and

digit recall. A tone indicated to the participants that they should recall out loud the digit sequence in the same order as it had previously been presented.

Immediate visual pattern span. Participants were presented with black and white chequered patterns containing an equal number of black and white squares [32]. To avoid verbal encoding of the patterns, they did not resemble recognizable shapes such as letters or numbers. The patterns were presented for 3 seconds before being removed. Participants were then given the same grid but blank, and had to mark on it the previously filled squares. There were no time limits for recall. In the first instance, participants were presented with three patterns containing two black and two white squares. If participants correctly recalled one of the three patterns, the pattern size increased by one black and one white square. The assessment continued until participants were unable to recall the black squares on all three trials at a given level. The mean pattern size for the last three correctly recalled patterns was considered the immediate visual pattern span.

Delayed visual pattern span. Delayed visual pattern span was calculated using the same procedure as immediate visual pattern span with the exception of pattern recall taking place 15 seconds after the removal of the visual pattern presented.

Immediate and Delayed Single Task.

Single task performance was then measured for immediate digit recall, delayed digit recall, immediate visual pattern recall and delayed visual pattern recall performed at the participant's individual ability level. For immediate digit recall and immediate visual pattern recall, participants performed 6 trials for each condition where they had to immediately recall at-span digit sequences or at-span visual pattern grids. For delayed

digit recall and delayed visual pattern recall, participants recalled the at-span digit sequence or visual pattern after a 15 second delay. The dependent variable for digit recall was the percentage of correctly recalled digits in the correct position within the sequence and the dependent variable for visual pattern recall was the percentage of correctly recalled squares in the correct position in the visual pattern. Again, there were 6 trials for each delayed single task condition.

Immediate and Delayed Dual Task.

To assess dual task performance, participants performed two dual task combinations where the following tasks were performed concurrently: 1) delayed digit recall (preload task) with immediate visual pattern recall (interpolated task); and 2) delayed visual pattern recall (preload task) with immediate digit recall (interpolated task). For each trial, the preload stimuli were presented to be remembered over a 15 second delay before being recalled. During that delay, the interpolated task was performed. See Figure 1 for the two dual task combinations. When visual pattern recall was the interpolated task, participants typically had time to recall two patterns and when digit recall was the interpolated task, participants typically had time to recall two digit sequences. Six trials were performed for each dual task combination. As in the single task conditions, the percentage accuracy for the dual task digit recall and visual pattern recall conditions was calculated.

- Insert Figure 1 around here -

Individual abilities levels were always evaluated first, followed by the single task conditions and finally the dual task conditions. Within the dual task paradigm, the presentation order of the tasks within each phase was randomized across individuals (e.g., single task: immediate digit recall, delayed digit recall, immediate visual pattern recall and delayed visual pattern recall).

Statistical analyses

The performance of the carriers and non-carriers on the background neuropsychological measures was compared using independent samples t-tests when the data were normally distributed and nonparametric Mann-Whitney U-tests when the data were not normally distributed. As performance on the immediate and delayed digit recall and visual patterns under dual task conditions was not normally distributed, nonparametric Mann-Whitney U-tests were conducted to compare the two groups. Separate Wilcoxon signed ranks tests compared immediate single and dual task performance (for the interpolated tasks) and delayed single and dual task performance (for the preload tasks) for each group. Spearman correlation coefficients were calculated to examine the relationships between dual task performance and performance on the background measures.

Receiver Operating Characteristics (ROC) analysis was also performed with those variables showing large and significant effects in the above mentioned analyses. This analysis was specifically aimed at identifying whether group differences found with these variables were also representative at the individual level. ROC driven cut-off values are

more reliable for classifying individuals within group categories as they are drawn from curves which help visualize and understand the trade-off between high sensitivity and high specificity when discriminating between clinically normal and clinically abnormal populations [33].

RESULTS

Background neuropsychological measures

The means and standard deviations for the carriers and non-carriers on the background neuropsychological tests are shown in Table 2. In terms of episodic memory performance, the carriers performed significantly more poorly than the non-carriers on the serial verbal learning recall task where a list of 10 common nouns is presented until participants can successfully recall all 10 words with a maximum of 10 repetitions: maximum words recalled in last trial (carrier median = 8.00, non-carrier median = 10.00), number of lists presented (carrier median = 6.00, non-carrier median = 4.50) and delayed recall 15-20 minutes later (carrier median = 4.00, non-carrier median = 5.00). However, no significant differences were found on the other episodic memory measures which included memory for words, paired-associates or recall of the Rey-Osterrieth Complex Figure. Therefore, the carriers demonstrated amnesic deficits on only one of the four episodic memory measures and neither the carriers nor their relatives reporting any subjective complaints of memory difficulties. In addition, the carriers did not perform

significantly more poorly than the non-carriers on any of the background measures of intellect, naming, arithmetic, executive function or speed of processing.

- Insert Table 2 about here -

Dual task paradigm

Evaluation of Individual Ability. The individual immediate and delayed digit span and visual pattern span means and standard deviations for the carriers and non-carriers are in Table 3. The two groups did not significantly differ in terms of any of their spans: immediate digit span (carrier median = 4.00, non-carrier median = 4.00), immediate visual pattern span (carrier median = 4.00, non-carrier median = 4.50), delayed digit span (carrier median = 5.00, non-carrier median = 4.00) or visual pattern span (carrier median = 5.00, non-carrier median = 4.00).

- Insert Table 3 about here -

Immediate and Delayed Single Task. The mean percentage accuracy and standard deviations for immediate and delayed digit recall and visual pattern recall are shown in Table 4. Separate Mann-Whitney U-Tests revealed that the preclinical carriers recalled significantly fewer digits and significantly fewer squares than the non-carriers when recall was both immediate (carrier median = 95.83, non-carrier median = 100.00, $U = 817.50$; $z = 3.10$; $p < .005$ and carrier median = 91.66, non-carrier median = 97.42, $U =$

890.00 ; $z = 3.71$; $p < .0001$ respectively) and delayed (carrier median = 91.66, non-carrier median = 100.00, $U = 893.00$; $z = 3.77$; $p < .0001$ and carrier median = 90.00, non-carrier median = 97.56, $U = 899.00$; $z = 3.82$; $p < .0001$ respectively).

Delayed digit recall (preload task) with immediate visual pattern recall (interpolated task). In terms of dual task performance, the preclinical carriers recalled significantly fewer digits than the non-carriers under delayed recall conditions (carrier median = 70.83, non-carrier median = 93.33, $U = 1130.50$; $z = 6.55$; $p < .0001$). They also recalled significantly fewer squares than the non-carriers under immediate recall conditions (carrier median = 77.77, non-carrier median = 94.72, $U = 958.50$; $z = 4.46$; $p < .0001$). Additional separate analyses comparing single and dual task delayed digit recall performance and single and dual task immediate visual pattern recall performance for each group revealed that both carriers and non-carriers showed a significant dual task drop in performance on both tasks: delayed digit recall ($z = -4.78$, $p < .0001$, $z = -3.81$, $p < .0001$ respectively) and immediate visual pattern recall ($z = -4.27$, $p < .0001$, $z = -3.63$, $p < .0001$ respectively).

As the carriers and non-carriers significantly differed in terms of their single task performance, the two groups were compared on their dual task performance using a Univariate Analysis of Covariance (ANCOVA) with single task performance entered as a covariate. Since the data were not normally distributed, a bootstrapping procedure with 1,000 bootstrap resamples and 95% confidence intervals (CI) was performed on the data. The bootstrap results showed that carriers still recalled significantly fewer digits under delayed recall conditions ($F(1, 66) = 45.07$, $p < .0001$) and significantly fewer squares

under immediate recall conditions than non-carriers ($F(1, 66) = 10.60, p < .005$) even when single task performance was controlled for.

Delayed visual pattern recall (preload task) with immediate digit recall (interpolated task). Under delayed recall conditions, the pre-clinical carriers correctly recalled significantly fewer squares than the non-carriers (carrier median = 72.22, non-carrier median = 93.33, $U = 1027.50; z = 5.30; p < .0001$). Digit recall also resulted in significantly fewer digits being correctly recalled by the pre-clinical carriers compared to the non-carriers under immediate recall conditions (carrier median = 84.61, non-carrier median = 95.83, $U = 940.00; z = 4.24; p < .0001$). When single and dual task performance for the preload and interpolated tasks was compared independently for the carrier and non-carrier groups, both groups showed a significant dual task drop under dual task conditions for both delayed visual pattern ($z = -4.49, p < .0001, z = -4.60, p < .0001$ respectively) and immediate digit recall ($z = -4.46, p < .0001, z = -4.71, p < .0001$ respectively). Table 4 demonstrates the mean percentage accuracy and standard deviations for the two groups performing under dual task conditions.

- Insert Table 4 about here -

To account for the differences in single task performance, separate ANCOVAs were conducted on the dual task performance of the two groups on the preload and interpolated tasks with single task performance entered as a covariate. The bootstrap results confirmed that the carriers and non-carriers still significantly differed in terms of

their dual task performance on delayed visual pattern recall ($F(1, 66) = 27.70, p < .0001$) and immediate digit recall ($F(1, 66) = 14.92, p < .0001$), even when single task performance was controlled for.

Overall dual task change. The overall percentage change in accuracy performance was calculated for each participant according to the formula in Figure 2. A score of 100 indicates no change in performance between single and dual task conditions, a score above 100 means there is an improvement during dual tasking and a score below 100 signifies there is a decline in performance when dual tasking. The overall change for both dual task paradigms is shown in Figure 2. Mann-Whitney U-tests showed a significant main effect of group where the preclinical carriers showed a significantly greater dual task cost than non-carriers in both delayed digit recall with immediate visual pattern recall (carrier median = 81.45, non-carrier median = 96.86, $U = 1075.00, z = 5.86, p < 0.0001$) and delayed visual pattern recall with immediate digit recall (carrier median = 84.22, non-carrier median = 96.70, $U = 952.00, z = 4.38, p < 0.0001$). A Spearman's correlation coefficient was calculated to determine the relationship between the preclinical carriers' overall change scores for the two dual task paradigms (i.e., delayed digit recall with immediate visual pattern recall compared with delayed visual pattern recall with immediate digit recall). A significant positive correlation was found which was statistically significant ($r_s(29) = .42, p < .05$).

- Insert Figure 2 about here -

Correlational analyses

To examine whether there are any significantly relationships between overall dual task change and performance on the background measures in preclinical carriers, Spearman correlation coefficients were calculated (see Table 5). Significant positive correlations were found between both overall dual task change scores and immediate recall on the Rey-Osterrieth Complex Figure suggesting that poor dual task performance is associated with poor visuospatial memory. There was also a significant positive correlation between the delayed visual pattern recall with immediate digit recall paradigm and learning recall on paired-associate learning suggesting that poor performance on this dual task paradigm is associated with poor learning recall. Finally, there was a significant negative correlation between the delayed visual pattern recall with immediate digit recall paradigm and time taken on the cancellation As task suggesting that poor dual task performance using this paradigm is associated with slower processing speed.

- Insert Table 5 around here -

ROC analyses

ROC analysis was conducted to obtain the optimal cut-off values (i.e., leading to highest sensitivity and specificity) that would correctly classify carriers and non-carriers into their corresponding groups using performance on the delayed digit recall with immediate visual pattern recall, delayed visual pattern recall with immediate digit recall

and delayed recall on the serial verbal learning recall task. Table 6 and Figure 3 show the results of this area under the curve analysis. This confirmed that the delayed digit recall and immediate visual pattern recall dual task paradigm and the delayed visual pattern recall and immediate digit recall dual task paradigm combined more sensitivity and specificity for carriers than delayed serial verbal learning. A score below 89.97% in the delayed digit recall with immediate visual pattern recall was 8.45 times (i.e., likelihood ratio) more likely to identify carriers of the mutation than controls. The best cut-off value for the delayed serial verbal learning recall task only was only 3.16 times more likely to identify carriers of the mutation than controls.

- Insert Table 6 and Figure 3 about here -

DISCUSSION

Individuals in the early stages of sporadic AD have previously been reported to show significant dual task decrements [1,2,6,7]. More recently, these dual task decrements have also been shown in familial AD due to a mutation in the E280A presenilin-1 gene as well as carriers of the genetic mutation who do not yet meet the criteria for AD [10]. The current study aimed to examine whether this carrier-related dual task decrement can be explained in terms of a deficit in the mechanism responsible for performing two tasks concurrently or whether it is specific to the task combination adopted in MacPherson et al. [10]. Indeed, when carriers and non-carriers of the genetic mutation were compared on the current dual task paradigm, combining two memory tasks

yielded significantly larger dual task costs in carriers than the non-carriers. These results fit with the notion of preclinical FAD disrupting the general ability to coordinate two tasks simultaneously.

Although the carriers of the genetic mutation did not subjectively report any memory complaints, some individuals did show impairment on the serial verbal learning recall task. Nevertheless, these episodic memory impairments were not consistent across measures as the carriers did not show impairments on the memory for words, paired associate learning and immediate recall of the Rey-Osterrieth Complex Figure tasks. Our previous work has shown that even carriers who do not show memory impairments can be classified as carriers using a dual task paradigm involving digit recall and tracking with acceptable levels of sensitivity (68%) and specificity (72%) [10]. In the current study, both dual task paradigms involving two memory tasks combined more sensitivity and specificity for carriers of the genetic mutation for FAD than the delayed serial verbal learning recall task. This current dual tasking approach boosted the classification power considerably bringing sensitivity to 74.4% and 86.67% and specificity to 85% and 89.74%. While these findings demonstrate that delayed serial verbal learning recall can successfully identify carriers of the genetic mutation, dual tasking provides a significant improvement in preclinical detection of carriers that had no cognitive complaints and were unaware of their health status by the time of testing. Therefore, dual task performance may be a suitable preclinical marker for individuals who will go on to develop FAD, even before episodic memory deficits are manifested.

The dual task impairment reported in our preclinical carriers is thought to be due to the coordination of two concurrent tasks rather than simply overloading memory.

Previously we have shown that increasing load does not underlie the dual task impairment found in AD patients. Logie et al. [4] increased the demands of the digit recall and tracking tasks when they were performed singly and concurrently. They found that increasing the single task demands of the tasks had comparable effects in AD patients and healthy adults and no interaction between dual task demands and decrements was found. Therefore, the dual-task impairment reported in sporadic AD is thought to be associated with working memory rather than episodic memory impairments but further work is required to determine whether this is also the case in carriers of the FAD genetic mutation.

Although the current study attempted to equate the carrier and non-carrier groups for their single task performance on both memory tasks, the carrier groups performed significantly more poorly than the non-carriers under single and dual task conditions. It may be that the procedure for task titration typically used in our dual task work is not as sensitive in familial AD. Here the carrier group is at a much earlier stage of their disease and they have considerably fewer years of education compared to our previous patient groups. It should also be noted that the groups had lower than normal IQ on a Spanish language version of the Wechsler Adult Intelligence Scale – III [22] which has been normalized in Colombia using different age and education groups [34-38]. Research has shown that low socio-cultural background, including education and illiteracy, can affect performance on neuropsychological tests [39-42] with education differences of even one or 2 years affecting performance [43]. Populations from countries where individuals are poorly educated pose a challenge for neuropsychological assessment and should be treated with caution. However, while it could be argued that the dual task decrements

found are simply inflated single task differences, when dual task performance was compared across the groups and single task performance was statistically controlled for, the dual task difference remained. This suggests that the dual task impairments found in our carrier groups are distinct from their single task differences.

As the carriers did not significantly differ from the non-carriers in terms of their MMSE scores (range 26-30), this implies that dual tasking is not associated with disease severity as assessed using the MMSE. Indeed, our previous work has also shown that dual task performance in both sporadic and familial AD is not associated with scores on the MMSE (e.g., [6,10]). Of course, the MMSE has been demonstrated to have poor sensitivity to mild cognitive impairment [44-48]. Therefore, one cannot categorically conclude that dual task performance is not related to dementia severity, at least not in less severe individuals.

As the carriers did not show poorer performance compared to the non-carriers on the other background neuropsychological tests included in the study such as intellect, executive function or speed of processing, dual task impairment would not appear to be linked with these other cognitive processes. Correlational analyses between the dual task overall change scores and the majority of these background neuropsychological tests did not reveal significant correlations in the preclinical carrier group. A significant positive correlation was found between dual task performance and the Rey-Osterrieth Complex Figure, which may be explained by the visuospatial memory component of this task and the Visual Pattern Test. The other significant correlations were not consistently found for both dual task paradigms. Future work should directly examine the relationship between dual task performance in AD and performance on other neuropsychological measures.

Familial AD due to the E280A presenilin-1 mutation is thought to be comparable with late-onset sporadic AD in terms of the majority of its features [11]. For that reason, carriers of the genetic mutation who are not yet displaying clinical characteristics of FAD could be considered the equivalent of pre-mild cognitive impairment in sporadic AD in terms of disease severity. Therefore, the dual task paradigm may be suitable for detecting cognitive change in individuals who will convert to sporadic AD with time. While significant dual task decrements have been reported in some studies of mild cognitive impairment (MCI) associated with sporadic AD compared to healthy controls [3,49,50], there are also other studies that have not reported MCI-related dual task costs [51-53]. Foley, Kaschel, Logie, & Della Sala [54] propose that MCI individuals who perform poorly when dual tasking are more likely to convert to AD compared to those who perform well (see also [55]). It could also be that the preclinical dual task impairment associated with the E280A mutation in the presenilin-1 gene is specific to this type of FAD rather than being a general indicator of early AD. Indeed, previous research has suggested that there may be phenotypic differences between familial and sporadic AD [56,57]. Future work using a longitudinal design to assess MCI conversion to AD and dual task performance is necessary to test the hypothesis of dual tasking being a preclinical marker of AD.

A potential confound is the contribution of depression to poor dual tasking performance in our carriers of the genetic mutation. Clinically, it remains difficult to differentiate between early AD and depression [58-62]. However, our participants were all blind to their genetic status and did not differ from the non-carriers in terms of their level of depression. In any case, our work has shown that individuals who suffer from

chronic depression do not demonstrate significant dual task impairments, even when they are equated for performance on episodic memory measures with AD patients [63].

In summary, carriers of the E280A presenilin-1 gene mutation, who do not yet meet the criteria for AD, demonstrate significant dual task costs when they are asked to perform two tasks simultaneously (see also [10]). This is despite performing well on other background neuropsychological tests and the majority of episodic memory tasks administered. Our previous work has demonstrated that the failure to perform two tasks simultaneously in sporadic AD is due to a fundamental deficit in coordination rather than the specific combination of tasks performed at the same time [1,2,4,6,64,65]. The current findings demonstrate that this same deficit in coordination is found in FAD.

ACKNOWLEDGEMENTS

M.A.P. work is supported by Alzheimer's Society, Grant # AS-R42303. The study is also sponsored by Colciencias, Grants 1115-408-20512 and 1115-343-19127 awarded to the Neuroscience Group, University of Antioquia, Colombia in collaboration with M.A.P. and S.D.S. The project was also partially supported by ALFA Eurocaribbean Neurosciences Network, contract AML/B7-311/97/0666/II-0322-FA-FCD-FI-FC, in which S.D.S. and F.L. were partners. This work was conducted within the context of The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (MR/K026992/1).

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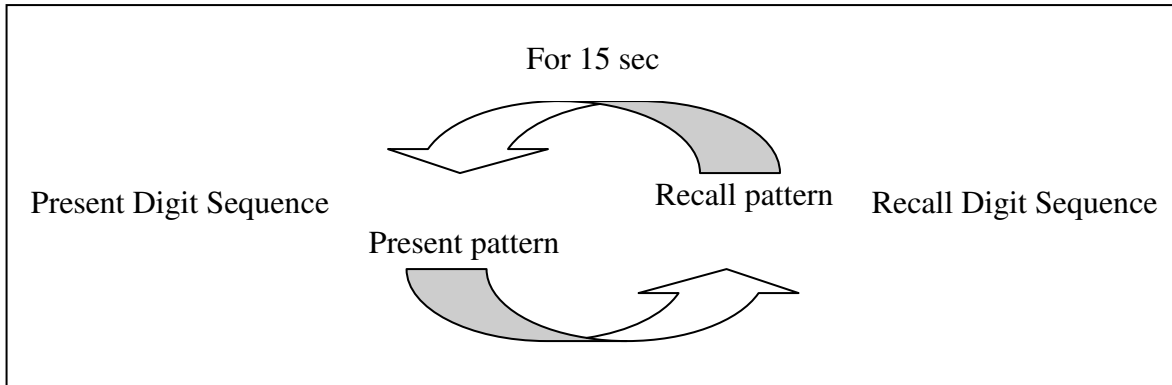
FIGURE CAPTION

Figure 1. The dual task combinations for the preload and interpolated tasks.

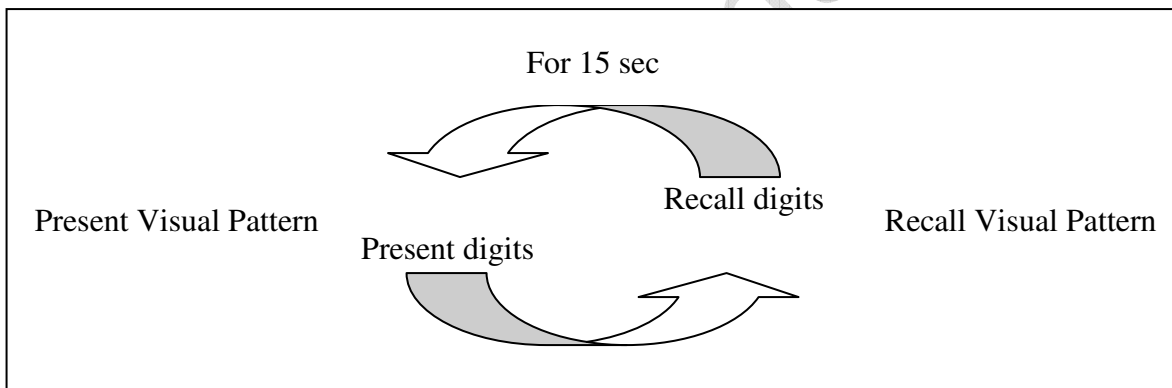
Figure 2. Overall mean percentage change (with standard error bars) between single and dual task performance in digit recall and visual pattern recall combined.

Figure 3. ROC analysis involving the performance on the two dual task paradigms and delayed serial verbal learning recall for carriers and non-carriers.

Digits + Patterns



Patterns + Digits

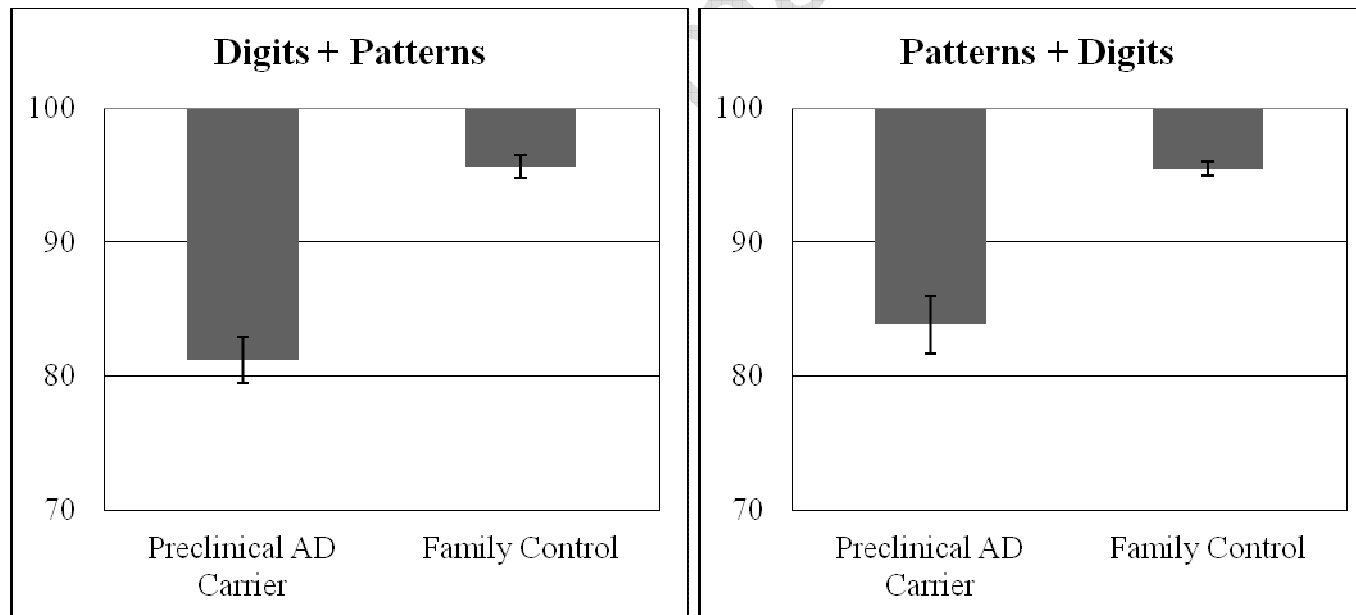


The percentage change for each test was calculated separately:

$$\text{Percent change} = \frac{\text{Single task performance} - \text{dual task performance}}{\text{Single task performance}} \times 100$$

Then the percentage change for each test was combined as follows:

$$\text{Combined percent change} = 100 - \frac{(\text{Percent change digit task} + \text{Percent change visual pattern task})}{2}$$



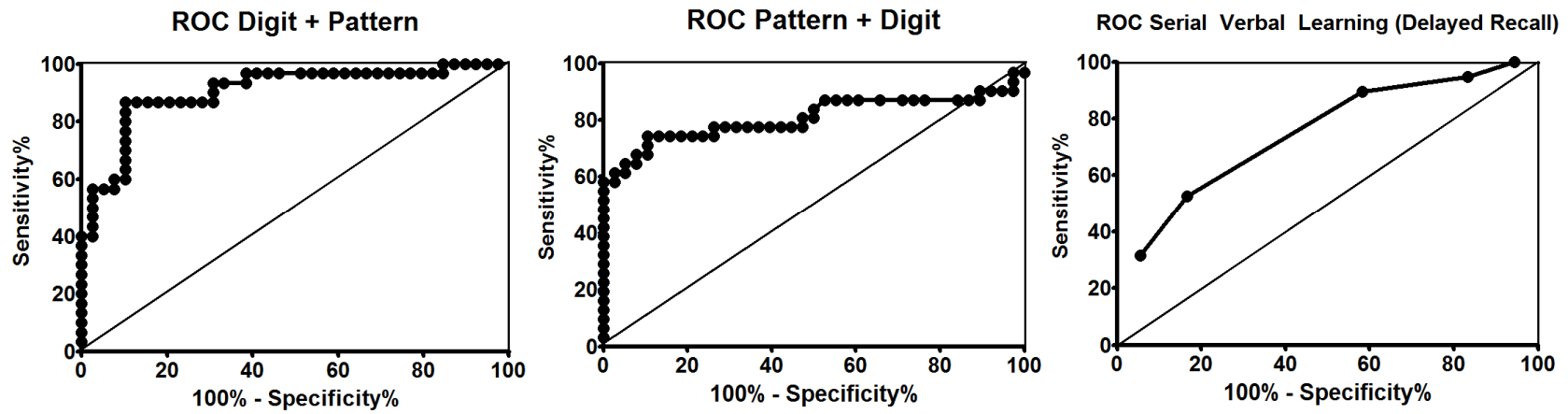


Table 1. Means and standard deviations in parentheses for the demographic characteristics of the carriers and non-carriers.

	<u>Carriers</u>		<u>Non-Carriers</u>			
	(n = 31)		(n = 38)			
	<u>Mean</u>	<u>SD</u>	<u>Mean</u>	<u>SD</u>	<u>t</u>	<u>p</u>
Age	35.45	6.33	38.03	8.10	-1.45	n.s.
Years of Education	9.77	4.33	9.47	3.45	0.32	n.s.
Gender (Male/Female)	9/22		8/30		0.59 ^a	n.s.
MMSE (max = 30)	29.41	0.73	29.54	0.85	1.18 ^b	n.s.
Yesavage Geriatric	1.62	3.01	1.72	2.87	0.11 ^b	n.s.
Depression Scale (max=15)						

^aChi-square statistic; ^bMann-Whitney U-Test z score

Table 2. Means and standard deviations in parentheses for the background measures performed by the carriers and non-carriers.

	<u>Carriers</u>		<u>Non-Carriers</u>			
	(n = 31)		(n = 38)			
	<u>Mean</u>	<u>SD</u>	<u>Mean</u>	<u>SD</u>	<u>Test</u>	<u>p</u>
					<u>Statistic</u>	
Serial Verbal Learning						
Maximum Words Recalled (max = 10)	8.35	1.70	9.66	1.24	868.00#	<.0001
Number of Lists Presented (max = 10)	6.48	2.71	4.82	1.97	2.87*	<.01
Delayed Recall (max = 10)	4.32	1.16	5.42	1.18	-3.31*	<.005
Memory for Words						
Total Recall (max = 30)	18.76	4.52	20.51	3.09	-1.84*	n.s.
Delayed Recall (max = 10)	6.90	2.18	7.69	1.47	-1.66*	n.s.
Paired Associates						
Total Score (max = 21)	12.47	3.58	13.99	3.55	-1.76*	n.s.
Learning Recall Difficult Items (max = 8)	4.77	3.07	6.05	3.17	-1.69*	n.s.
Rey-Osterrieth Complex Figure Immediate Recall (max = 36)	15.84	5.51	16.10	6.80	-0.17*	n.s.
WAIS Full-Scale IQ	88.93	10.45	91.34	11.87	621.00#	n.s.
Raven's APM Part A (max = 12)	9.48	1.78	9.15	1.69	394.50#	n.s.
Boston Naming (max = 15)	13.59	0.98	12.94	1.71	413.00#	n.s.

WAIS Arithmetic (max = 10)	8.89	1.34	8.50	1.48	385.50#	n.s.
Verbal Fluency Total Words (Letter F)	12.07	4.99	11.83	4.44	0.20*	n.s.
M-WCST Perseverative Errors (max = 48)	13.93	6.38	12.83	5.65	0.73*	n.s.
Trail Making Part A Time (seconds)	59.43	35.52	54.91	24.75	471.00#	n.s.
Cancellation As Time (seconds)	35.30	15.87	31.82	10.45	418.00#	n.s.

WAIS = Wechsler Adult Intelligence Scale; APM = Advanced Progressive Matrices; M-

WCST = Modified Wisconsin Card Sorting Test

* = Independent Samples T-test; # = Mann-Whitney U-Test

Table 3. Means and standard deviations in parentheses for the carriers' and non-carriers' immediate and delayed digit spans and immediate and delayed visual pattern spans.

	<u>Carriers</u>		<u>Non-Carrier</u>			
	(n = 31)		(n = 38)			
	<u>Mean</u>	<u>SD</u>	<u>Mean</u>	<u>SD</u>	<u>Test</u>	<u>p</u>
					<u>Statistic</u>	
Immediate digit span	4.58	0.89	4.37	0.68	505.00	n.s.
Delayed digit span	4.74	0.82	4.39	0.76	1.83*	n.s.
Immediate VPT span	4.52	1.36	4.76	1.38	628.50	n.s.
Delayed VPT span	4.71	1.47	4.97	1.59	624.50	n.s.

* = Independent Samples T-test; # = Mann-Whitney U-Test

Table 4. Mean percentage accuracy with standard deviations in parentheses for digit recall and visual pattern recall under single and dual task conditions for carriers and non-carriers.

	<u>Carriers</u>		<u>Non-Carriers</u>	
	(n = 31)		(n = 38)	
	<u>Mean</u>	<u>SD</u>	<u>Mean</u>	<u>SD</u>
Single task				
Immediate digit recall	93.61	7.36	97.92	4.26
Delayed digit recall	90.23	8.12	96.85	4.12
Immediate visual pattern recall	90.39	8.16	96.75	3.93
Delayed visual pattern recall	89.60	8.12	96.11	5.29
Dual task				
Immediate digit recall	82.42	11.85	93.54	5.51
Delayed digit recall	68.76	16.06	92.98	4.82
Immediate visual pattern recall	78.10	13.97	91.93	7.65
Delayed visual pattern recall	71.07	16.75	91.67	6.78

Table 5. Spearman's correlations between overall dual task performance and performance on the background measures in pre-clinical carriers.

	<u>Delayed</u>	<u>Delayed Visual</u>
	<u>Digits/Immediate</u>	<u>Patterns/Immediate</u>
	<u>Visual Patterns</u>	<u>Digits</u>
MMSE	.15	.20
Serial Verbal Learning		
Maximum Words Recalled	-.09	.08
Number of Lists Presented	-.002	-.32
Delayed Recall	.10	.37
Memory for Words		
Total Recall	.09	.17
Delayed Recall	.13	.14
Paired Associates		
Total Score	.30	.30
Learning Recall Difficult Items	.34	.42*
Rey-Osterrieth Complex Figure	.42*	.52**
Immediate Recall		
WAIS Full-Scale IQ	-.02	.25
Raven's APM Part A	.16	.29
Boston Naming	.11	.25
WAIS Arithmetic	-.21	.05
Verbal Fluency Total Words	.15	.20
M-WCST Perseverative Errors	-.06	-.34
Trail Making Part A Time	.08	-.08
Cancellation As Time	.10	-.43*

*p < .05, ** p < .01

Table 6. ROC analysis with the two dual task paradigms and delayed verbal learning across the two groups.

	Cut-off	Sensitivity	95% CI	Specificity	95% CI	Likelihood ratio
Delayed digit recall + Immediate VPT	<89.97	86.67	69.28% to 96.24%	89.74	75.78% to 97.13%	8.45
Delayed VPT + Immediate digit recall	< 92.64	74.19	55.39% to 88.14%	81.58	65.67% to 92.26%	4.03
Serial Verbal Learning - Delayed	< 4.500	52.63	28.86% to 75.55%	83.33	67.19% to 93.63%	3.16

Likelihood ratio = Sensitivity/(1-Specificity); VPT = Visual Pattern Test;